Complete Summary

GUIDELINE TITLE

Newer drugs for epilepsy in adults.

BIBLIOGRAPHIC SOURCE(S)

National Institute for Clinical Excellence (NICE). Newer drugs for epilepsy in adults. London (UK): National Institute for Clinical Excellence (NICE); 2004 Mar. 36 p. (Technology appraisal; no. 76).

GUIDELINE STATUS

This is the current release of the guideline.

** REGULATORY ALERT **

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse (NGC): This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

On April 19, 2005, Novartis Pharmaceuticals and the U.S. Food and Drug Administration (FDA) notified healthcare professionals about revisions to the WARNINGS and PRECAUTIONS sections of the prescribing information for TRILEPTAL (oxcarbazepine) tablets and oral suspension, indicated for use as monotherapy or adjunctive therapy in the treatment of partial seizures in adults and children ages 4-16 years with epilepsy. The updated WARNINGS section describes serious dermatological reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) that have been reported in both children and adults in association with Trileptal use. The PRECAUTIONS section has been updated to include language regarding multi-organ hypersensitivity reactions that have been reported in association with Trileptal use. See the FDA Web site for more information.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Epilepsy

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Family Practice
Internal Medicine
Neurology

INTENDED USERS

Advanced Practice Nurses
Physician Assistants
Physicians

GUIDELINE OBJECTIVE(S)

To assess the clinical and cost-effectiveness of the newer antiepileptic drugs gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate and vigabatrin for the management of epilepsy in people who have not benefited from treatment with the older antiepileptic drugs

TARGET POPULATION

Adults with epilepsy who have not benefited from treatment with the older antiepileptic drugs

INTERVENTIONS AND PRACTICES CONSIDERED

1. Antiepileptic drug treatment as monotherapy or combination therapy:
    - Gabapentin
    - Lamotrigine
    - Levetiracetam
    - Oxcarbazepine
    - Tiagabine
    - Topiramate

    - Vigabatrin
2. Assessment of risks and benefits of drugs in women of child-bearing potential
3. Referral to specialists in persons with first seizure
4. Review of and monitoring of treatment

MAJOR OUTCOMES CONSIDERED

- Clinical effectiveness, primarily:
    - Proportion of seizure-free participants
    - Proportion of participants experiencing at least a 50% reduction in seizure frequency (i.e., responders)
    - Time to exit/withdrawal
    - Time to first seizure
    - All quality of life outcomes
    - All outcomes relating to cognitive function
    - Safety (incidence of adverse events, mortality rate) and tolerability (incidence of withdrawals)
- Cost-effectiveness

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases
Searches of Unpublished Data

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Clinical Excellence (NICE) commissioned an independent academic centre to perform a systematic literature review on the technology considered in this appraisal and prepare an assessment report. The assessment report for this technology appraisal was prepared by the Centre for Reviews & Dissemination (CRD)/Centre for Health Economics (CHE) University of York (see the "Companion Documents" field).

Assessment of Clinical Effectiveness

Search Strategy

The following sources were searched for studies relating to the clinical effectiveness of newer antiepileptic drugs (AEDs); lamotrigine, gabapentin, levetiracetam, oxcarbazepine, tiagabine, topiramate and vigabatrin. This first set of literature searches were designed to retrieve systematic reviews and randomised controlled trials only. However, some databases cannot be reliably restricted by study type and in these cases the search was not limited by study design, and the results of the searches were screened by hand. A range of free text terms and subject headings were used as appropriate. Further details of the search strategies are reported in Appendix 2 of the assessment report.

CRD Internal Administration Databases (searched 20.03.02)

- Database of Abstracts of Reviews of Effective (DARE)
- Health Technology Assessment Database (HTA)

Internet Resources and Databases (searched 02.04.02)

- Controlled Clinical Trials http://controlled-trials.com
- Health Evidence Bulletins Wales http://hebw.cf.ac.uk/
- Health Services Technology Assessment Text (HSTAT) http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=hstat
- Index to Scientific and Technical proceedings (ISTP) http://wos.mimas.ac.uk/
- National Coordinating Centre for Health Technology Assessment http://www.hta.nhsweb.nhs.uk
- National Guideline Clearinghouse http://www.guideline.gov
- National Institute for Clinical Excellence (NICE) (published appraisals) http://www.nice.org.uk/
- Science Citation Index (SCI) (1981 - onwards) http://wos.mimas.ac.uk/
- Scottish Intercollegiate Guidelines Network (SIGN) Guidelines http://www.sign.ac.uk/
- Turning Research Into Practice (TRIP) Index http://www.update-software.com/trip/logon.asp?Log=1&SrchEx=_SrchEx_

CD-ROM Resources

- Cochrane Controlled Trials Register (CCTR) (2002: Issue 1) (searched: 02/04/02)
- Cochrane Database of Systematic Reviews (CDSR) (2002: Issue 1) (searched: 02/04/02)
- EMBASE (1980 - 2002/02) (searched: 27/03/02)
- MEDLINE (1966 - 2002/03) (searched: 26/03/02)
- National Research Register (NRR) (2002: Issue 1) (searched: 02/04/02)
- PREMEDLINE (up to 22.03.02) (searched: 26/03/02)
- PsycINFO (1967 - 2002/07 Week 3) (searched: 03/09/02)

Online Resources (searched: 08/04/02)

- Conference Papers Index (CPI) (1973 onwards)

Paper Resources

- Clinical Evidence: A compendium of the best available evidence for effective health care. Issue 6, 2001. London: BMJ Publishing Group.

No date or language restrictions were placed on any of the literature searches. Due to financial and logistical constraints non-English publications were not included in the review. However, not limiting the literature searches by language enabled an estimate of the size of the non-English literature to be obtained. In addition, search strategies were not limited by age although the review only included data relating to adults. This was due to the fact that many records do not mention the appropriate patient group within the title, abstract or indexing. The

bibliographies of all included studies were reviewed in order to identify any further relevant studies. A list of studies found from bibliographies and industry submissions, but not meeting the inclusion criteria for this review, are listed in Appendix 3 of the assessment report.

Inclusion and Exclusion Criteria

Two reviewers independently screened all titles and abstracts in order to determine relevance. Full paper manuscripts of potentially relevant titles and abstracts were obtained where possible and the eligibility of the study for inclusion in the review was assessed by two authors independently, according to the four criteria outlined below. Any discrepancies were resolved by consensus and if necessary a third reviewer was consulted. Studies that did not fulfill all of the criteria were excluded. Due to time and financial constraints only studies reported in English were included in the analysis section of this review. Eligible studies in other languages were identified but only brief details tabulated.

Study Design

The following study designs were included in the review:

- Single-blinded, double-blinded or unblinded randomised controlled trials (RCTs) using a parallel or crossover design, designed to assess the equivalence, non-inferiority or superiority of comparators
- Systematic reviews meeting fulfilling the criteria for inclusion in the Database of Abstracts of Review of Effect (DARE) (http://www.york.ac.uk/inst/crd/darehp.htm

Participants

Studies recruiting adults (i.e., individuals aged 18 years or over) with either newly diagnosed or refractory epilepsy were included. Seizure types included partial onset (with or without secondary generalisation) and generalised onset seizures. Trials enrolling only patients with single seizures, status epilepticus, seizures following neurosurgery or head injury, and trigeminal neuralgia were excluded. Studies that enrolled participants with excluded indications were evaluated to determine whether: 1) the study results reported data for the excluded indications groups of participants separately, or 2) the numbers of excluded indications participants was small. In either case the relevant data was included in this review.

Studies with mixed age groups were identified during the inclusion/exclusion process. The data reported in these studies was discussed and divided accordingly in coordination with the Birmingham review team responsible for reviewing the evidence for the treatment of children. The discussion determined whether 1) the study results reported data for the different age groups of participants separately, or 2) the numbers of younger or older participants were small. Data were only extracted if relevant to age group under consideration.

Interventions

Newer antiepileptic drugs (AEDs) (gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate, and vigabatrin) used either, as monotherapy and/or adjunctive therapy were included. Comparators included older AEDs, newer AEDs, or placebo. Trials where epilepsy surgery was the comparator were excluded. Older AEDs included acetazolamide, benzodiazepines, carbamazepine, ethosuximide, phenobarbital and other barbiturates, phenytoin, and valproate.

Assessment of Serious, Rare and Long-Term Adverse Events Studies

Search Strategy

Literature searches were carried out to identify serious, rare and long-term adverse events not likely to have been found by the clinical effectiveness RCT search strategies. The searches aimed to find all possible side effects of these seven drugs irrespective of the condition treated. Therefore, no epilepsy terms were added. It is well reported in the literature that conducting electronic database searching for adverse events is problematic. The procedure for tracing papers of adverse events is not as well established as in other areas of research such as RCTs and systematic reviews. A broad experimental search strategy was therefore adopted using textwords, and thesaurus terms for each drug limited to the appropriate subheadings and known serious or rare side effects as both textwords and thesaurus terms. Those adverse events deemed serious fell into one or more of the following categories; death, life threatening, hospitalisation, disability (including vision), congenital abnormality, cancer, and overdose.

Databases were searched from the date of inception to the most recent date available.

Internet Resources and Databases (all searched 09/09/02)

- ABPI electronic Medicines Compendium (eMC) (Version 2). http://www.medicines.org.uk/
- Controlled Clinical Trials http://controlled-trials.com
- Developmental & Reproductive Toxicology (DART/ETIC) http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?DARTETIC
- Drug Checker - Interactions Search http://www.drugs.com/data/channel/md/drkoop.cfm?int=1://
- Drug facts and comparisons http://www.factsandcomparisons.com/index.aspx
- Emedicine http://www.emedicine.com/
- General Practice Notebook http://www.gpnotebook.co.uk
- Health Evidence Bulletins Wales http://hebw.cf.ac.uk/
- Health Services Technology Assessment Text (HSTAT) http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=hstat
- Index to Scientific and Technical proceedings (ISTP) http://wos.mimas.ac.uk/
- The Merck Manual http://www.merck.com
- National Coordinating Centre for Health Technology Assessment http://www.hta.nhsweb.nhs.uk
- National Guideline Clearinghouse http://www.guideline.gov
- National Institute for Clinical Excellence (NICE) (published appraisals) http://www.nice.org.uk/
- Science Citation Index (SCI) (1981 - onwards) http://wos.mimas.ac.uk/

- Scottish Intercollegiate Guidelines Network (SIGN) Guidelines http://www.sign.ac.uk/
- TOXLINE - Toxicology Bibliographic Information (1965 - PRESENT) http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?TOXLINE
- Turning Research Into Practice (TRIP) Index http://www.update-software.com/trip/logon.asp?Log=1&SrchEx=_SrchEx_

CD-ROM Resources (searched: 10/09/02)

- EMBASE (1980-2002 Week 36)
- MEDLINE (1996-August Week 4 2002)

Paper Resources (searched: 04/09/02)

- ABPI Medicines Compendium. Datapharm Communications Ltd. 2002.
- AHFSFirst professional edition version 2.71. American Society of Health-System Pharmacists. 2002.
- British National Formulary (BNF). London: British Medical Association/ Royal Pharmaceutical Society of Great Britain. Issue 43 March 2002,
- Dukes, M.N.G. and Aronson, J.K. (eds.). Meylers's Side Effects Of Drugs: An Encyclopedia of Adverse Reaction and Interactions. 14th edition. Oxford: Elsevier. 2000.
- Sweetman, S.C. (ed.) Martindale: the complete drug reference. 33rd edition. London: Pharmaceutical Press. 2002.

Further details of the full search strategy are reported in Appendix 2 of the assessment report.

Inclusion and Exclusion Criteria

In this review, non-randomised experimental studies and observational studies were included to enhance retrieval of information about serious, rare and long-term adverse events. Reporting of safety data in RCTs is largely inadequate and most systematic reviews of RCTs only include safety data as reported in the primary studies. Furthermore, RCTs are often too small and of insufficient duration to detect rare and delayed events. Consequently, evaluation of the safety of therapeutic interventions needs to go beyond RCTs.

Two reviewers independently screened all titles and abstracts against pre-defined inclusion criteria. Differences were resolved by discussion and full papers were obtained for all studies potentially eligible for inclusion. Two reviewers then independently applied the inclusion criteria to all full papers and differences were again resolved by discussion.

Three categories of studies were included:

- Studies that investigated the effects of newer AEDs, including safety and/or tolerability. Study designs eligible for inclusion were uncontrolled trials, open label extension phases of controlled trials, cohort studies (controlled or uncontrolled) and case-control studies. These studies, RCTs of newer AEDs in diseases other than epilepsy, and RCTs of dose or titration comparisons in

epilepsy, were included only if more than 300 participants were exposed to the newer AED or if follow up exceeded 6 months. These limits were based on the duration and size of effectiveness RCTs. Combination therapies and dose comparisons were included within the aforementioned parameters. Case series, case reports, cross-sectional studies, audits and surveys were excluded.
- Studies that investigated a specific adverse effect (such as visual field defects). Study designs eligible for inclusion were as described above but without the restriction on study size or duration.
- Reports of prescription event monitoring studies and prospective post-marketing surveillance studies. Spontaneous case reports of suspected adverse drug reactions such as those collated by the Medicines Control Agency and other bodies were not included.

Assessment of Cost Effectiveness

Search Strategy

Those databases restricted by study design in the clinical effectiveness searches were searched again using a search strategy designed to retrieve cost effectiveness studies or economic models. Two specialist databases were also searched, the National Health Service (NHS) Economic Evaluation Database (NHS EED) and the Health Economic Evaluation Database (HEED). No economic filter was necessary for these databases.

CRD Internal Administration Databases (searched 20.03.02)

NHS Economic Evaluation Database (NHS EED)

CD-ROM Resources

- EMBASE (1980 - 2002/02) (searched: 27/03/02)
- Health Economic Evaluation Database (HEED) (March 2002) (searched: 28/03/02)
- MEDLINE (1966 - 2002/03) (searched: 27/03/02)
- PREMEDLINE (up to 22.03.02) (searched: 27/03/02)

Further details of the search strategies used are reported in Appendix 2.

Inclusion and Exclusion Criteria

Three reviewers independently screened all of the titles and abstracts of the retrieved references according to following inclusion criteria. Any disagreements were resolved by consensus.

Study Design

Only full economic evaluations were included. Types of designs included:

- Cost-effectiveness analyses including cost-minimisation analyses and cost consequences analyses

- Cost-benefit analyses
- Cost-utility analyses

Participants

Studies recruiting adults (i.e., individuals aged 18 years or over) with either newly diagnosed or refractory epilepsy were included. Seizure types included both partial onset (with or without secondary generalisation) and generalised onset. Trials enrolling only patients with single seizures, status epilepticus, seizures following neurosurgery or head injury, and trigeminal neuralgia were excluded. Studies that enrolled participants with excluded indications were evaluated to determine whether: 1) the study results reported data for the excluded indications groups of participants separately, or 2) the numbers of excluded indications participants was small. Any relevant data were included.

Interventions

Newer AEDs (gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate, and vigabatrin) used either, as monotherapy and/or adjunctive therapy were included. Comparators included older AEDs, newer AEDs, or placebo. Trials where epilepsy surgery was the comparator were excluded. Older AEDs included acetazolamide, benzodiazepines, carbamazepine, ethosuximide, phenobarbital and other barbiturates, phenytoin, and valproate.

Outcomes

In order to be included in the review of cost effectiveness evaluations had to report both costs and clinical effectiveness.

NUMBER OF SOURCE DOCUMENTS

A total of 8095 titles and abstracts were screened for relevance and full copies of 1098 studies were ordered and assessed for inclusion/exclusion. A total of 212 studies were included in the review: 13 systematic reviews, 101 effectiveness publications covering 88 randomised controlled trials, 88 non-randomised experimental studies and observational publications covering 77 studies, and 21 economic evaluations.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Meta-Analysis of Randomized Controlled Trials
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Assessment of Clinical Effectiveness

Data Extraction Strategy

Data relating to study design, participants, interventions and outcomes were extracted in a standardised manner into an Access database by one reviewer and independently checked for accuracy by a second reviewer. Details of the types of data extracted are listed in Appendix 6 of the assessment report.

Attempts were made where possible to contact authors for missing data. Data from studies with multiple publications were extracted and reported as a single study. Where studies reported cognitive/quality of life data and seizure frequency outcomes in separate publications, both publications were considered.

Quality Assessment Strategy

Systematic Reviews

To be included in the review of effectiveness, as previously mentioned, all systematic reviews were required to meet the criteria necessary for inclusion in the Database of Abstracts of Reviews of Effects (DARE). Refer to Appendix 7 of the assessment report for the list of criteria used to assess the quality of systematic reviews. These criteria assess the quality of the review and so any reviews meeting the inclusion criteria were judged to be of reasonable quality. Assessment of the criteria was performed by one reviewer and independently checked by a second reviewer. Disagreements were resolved through consensus and if necessary a third reviewer was consulted.

Randomised Controlled Trials (RCTs)

The quality of the individual RCTs was assessed using criteria adapted from those used in the publication 'Undertaking Systematic Reviews of Research on Effectiveness: CRD's Guidance for Carrying Out or Commissioning Reviews'. In addition quality issues specifically pertaining to crossover and equivalence trials, were applied where appropriate. Refer to Appendix 8 of the assessment report for the list of criteria used to assess the quality of the individual RCTs.

In each case the quality of the trials was assessed by one reviewer and independently checked by a second reviewer. Disagreements were resolved through consensus and if necessary a third reviewer was consulted.

Handling Company Submissions

Data submitted by drug manufacturers by the deadline of 6th September 2002 were included. Submissions were checked for unpublished studies and any additional relevant information in relation to already published studies. Unpublished studies were assessed according to the inclusion/exclusion criteria above. Data extraction and quality assessment were carried out as for published

studies. No submissions were received from the manufacturers of gabapentin or vigabatrin.

Data Analysis

Systematic Reviews

Data identified from systematic reviews are summarised in table form and briefly discussed in relation to the requirements and findings of this current review.

Randomised Controlled Trials

Data from the randomised controlled trials were presented in tables and discussed in a narrative. Effect sizes (relative risks (RRs) or hazard ratios (HRs) with 95% confidence intervals (CIs)) were reported where appropriate. RRs and HRs were considered to be statistically significant if the range of the 95% CIs does not include 1. Data were only pooled statistically (fixed effects model) if studies were considered to be clinically and statistically (Q-statistic) homogeneous. Due to the low power of the Q-statistic where numbers of studies are small (i.e. less than 20), a p value of 0.10 was used as a threshold for statistical significance. Studies were only pooled using the fixed effects model if the Q-statistic was less than the degrees of freedom (df) and the associated p value greater than 0.10.

Assessment of Serious, Rare and Long-Term Adverse Events Studies

Data Extraction Strategy

One reviewer extracted data using a standardised data extraction form (see Appendix 9 of the assessment report). Adverse effects data were extracted in detail only for serious, rare and long-term effects, and for withdrawal or discontinuation of treatment due to adverse effects. Published sources were used for guidance on the nature of serious and rare events associated with the newer AEDs. Serious included death, life threatening, hospitalisation, disability, congenital abnormality, cancer and overdose. Both serious and rare included any effect defined as such in the study reports. Long term was defined as longer than 6 months.

Prescription event monitoring and prospective post-marketing surveillance studies were data extracted directly into summary tables by one reviewer.

Quality Assessment Strategy

Data on methodological quality were extracted by one reviewer using standardized data extraction forms. Cohort and case-control studies were assessed using criteria derived from Centre for Reviews & Dissemination (CRD) Report 4.17 (See Appendix 10 of the assessment report) RCTs, non-randomised and uncontrolled studies were assessed against the criteria used in the review of effectiveness (see Appendix 8 of the assessment report). Study design and methods of prescription event monitoring and prospective post-marketing surveillance studies were tabulated.

Handling Company Submissions

Data submitted by drug manufacturers by the deadline of 6th September 2002 was searched for relevant studies according to the aforementioned criteria. No submissions were received from the manufacturers of gabapentin or vigabatrin.

Data Analysis

Tables describing the included studies and a narrative summary were presented according for each drug.

Cost Effectiveness

Data Extraction Strategy

Data from each individual study were extracted into an Access database by one reviewer and checked by a second reviewer. Details of the categories of data extracted are presented in Appendix 11 of the original guideline document.

Quality Assessment Strategy

The quality of each published economic evaluation was assessed independently by two reviewers using the criteria listed in Appendix 12 of the assessment report. Appendix 13 of the assessment report lists the economic model with any associated quality issues. In both cases disagreements were resolved through discussion with a third reviewer if necessary.

Handling Company Submissions

Data submitted by drug manufacturers by the deadline of 6th September 2002 were included. Submissions were checked for unpublished economic evaluations and models. Such evaluations were subject to similar processes of study selection, data extraction, and data analysis as reported for published evaluations.

Data Analysis

Summary tables of the data within the included economic evaluations are presented along with a critical appraisal of the design and findings of each of the evaluations. In addition an overview and comparison of the models reported within the company submissions is presented, in order to assess the suitability of the evaluations for use in an integrated economic evaluation of all the newer AEDs.

Integrated Economic Evaluation

In order to determine the cost-effectiveness of the newer AEDs all of the relevant available treatments must be directly compared. As described in section 3.3 of the assessment report, none of the published evaluations or industry submissions represented a direct comparison of all of the newer and older AEDs specified in the scope for this review. Therefore a decision analytic model was developed which incorporated all of the available information on the cost-effectiveness of the

various newer and older AEDs that allowed direct comparisons to be made. The details of the structure of this analytic model, the information used to parameterise it, and the results of the analysis are described in section 3.4 of the assessment report. In summary, a cost-utility analysis was performed; using quality-adjusted life years calculated using utility weights estimated from EQ-5D responses and UK public valuations, so that the cost-effectiveness of the newer AEDs could be compared to the cost-effectiveness of treatments for other conditions.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Considerations

Technology appraisal recommendations are based on a review of clinical and economic evidence.

Technology Appraisal Process

The National Institute for Health and Clinical Excellence (NICE) invites 'consultee' and 'commentator' organisations to take part in the appraisal process. Consultee organisations include national groups representing patients and carers, the bodies representing health professionals, and the manufacturers of the technology under review. Consultees are invited to submit evidence during the appraisal and to comment on the appraisal documents.

Commentator organisations include manufacturers of the products with which the technology is being compared, the National Health Service (NHS) Quality Improvement Scotland and research groups working in the area. They can comment on the evidence and other documents but are not asked to submit evidence themselves.

NICE then commissions an independent academic centre to review published evidence on the technology and prepare an 'assessment report'. Consultees and commentators are invited to comment on the report. The assessment report and the comments on it are then drawn together in a document called the evaluation report.

An independent Appraisal Committee then considers the evaluation report. It holds a meeting where it hears direct, spoken evidence from nominated clinical experts, patients, and carers. The Committee uses all the evidence to make its first recommendations, in a document called the 'appraisal consultation document' (ACD). NICE sends all the consultees and commentators a copy of this document and posts it on the NICE website. Further comments are invited from everyone taking part.

When the Committee meets again it considers any comments submitted on the ACD; then it prepares its final recommendations in a document called the 'final appraisal determination' (FAD). This is submitted to NICE for approval.

Consultees have a chance to appeal against the final recommendations in the FAD. If there are no appeals, the final recommendations become the basis of the guidance that NICE issues.

Who is on the Appraisal Committee?

NICE technology appraisal recommendations are prepared by an independent committee. This includes health professionals working in the NHS and people who are familiar with the issues affecting patients and carers. Although the Appraisal Committee seeks the views of organisations representing health professionals, patients, carers, manufacturers and government, its advice is independent of any vested interests.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

The evidence on cost effectiveness considered by the Committee included an integrated cost-effectiveness analysis developed by the Assessment Group and economic evaluations submitted by the manufacturers of five of the drugs (lamotrigine, levetiracetam, oxcarbazepine, tiagabine and topiramate). The Assessment Group also provided a review of the published literature on the cost effectiveness of newer antiepileptic drugs.

See Section 4.2 of the original guideline document for a detailed discussion of the cost-effectiveness analysis.

METHOD OF GUIDELINE VALIDATION

External Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Consultee organizations from the following groups were invited to comment on the draft scope, Assessment Report and the Appraisal Consultation Document (ACD) and were provided with the opportunity to appeal against the Final Appraisal Determination.

- Manufacturer/sponsors
- Professional/specialist and patient/carer groups
- Commentator organisations (without the right of appeal)

In addition, individuals selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups were also invited to comment on the ACD.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

- The newer antiepileptic drugs gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate and vigabatrin, within their licensed indications, are recommended for the management of epilepsy in people who have not benefited from treatment with the older antiepileptic drugs such as carbamazepine or sodium valproate, or for whom the older antiepileptic drugs are unsuitable because:
    - there are contraindications to the drugs
    - they could interact with other drugs the person is taking (notably oral contraceptives)
    - they are already known to be poorly tolerated by the individual
    - the person is a woman of childbearing potential (see below).
- It is recommended that people should be treated with a single antiepileptic drug (monotherapy) wherever possible. If the initial treatment is unsuccessful, then monotherapy using another drug can be tried. Caution is needed during the changeover period.
- It is recommended that combination therapy (adjunctive or 'add-on' therapy) should only be considered when attempts at monotherapy with antiepileptic drugs (see above) have not resulted in seizure freedom. If trials of combination therapy do not bring about worthwhile benefits, treatment should revert to the regimen (monotherapy or combination therapy) that has proved most acceptable to the patient, in terms of providing the best balance between effectiveness in reducing seizure frequency and tolerability of side effects.
- In women of childbearing potential, the possibility of interaction with oral contraceptives and the risk of the drugs causing harm to an unborn child should be discussed and an assessment made as to the risks and benefits of treatment with individual drugs. There are currently few data upon which to base a definitive assessment of the risks to the unborn child associated with the newer drugs. Specific caution is advised in the use of sodium valproate because of the risk of harm to the unborn child.
- It is recommended that all people having a first seizure should be seen as soon as possible by a specialist in the management of the epilepsies to ensure precise and early diagnosis and initiation of therapy as appropriate to their needs.
- Treatment should be reviewed at regular intervals to ensure that people with epilepsy are not maintained for long periods on treatment that is ineffective or poorly tolerated and that concordance with prescribed medication is maintained.
- The recommendations on choice of treatment and the importance of regular monitoring of effectiveness and tolerability are the same for specific groups such as older people and those with learning disabilities as for the general population.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

Only randomised controlled trials and systematic reviews were included in the review of clinical effectiveness, and in addition non-randomised experimental studies and observational studies were included in the review of serious, rare and long-term adverse events.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate use of the newer epileptic drugs for the management of patients with epilepsy to decrease the frequency of attacks and improve quality of life

POTENTIAL HARMS

Adverse events associated with therapy, including the risk of the drugs causing harm to an unborn child and the possibility of interaction with oral contraceptives, For full details of side effects and contraindications, the reader is referred to the Summary of Product Characteristics for each antiepileptic drug.

CONTRAINDICATIONS

CONTRAINDICATIONS

For full details of contraindications, the reader is referred to the Summary of Product Characteristics for each antiepileptic drug.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

This guidance represents the view of the Institute, which was arrived at after careful consideration of the available evidence. Health professionals are expected to take it fully into account when exercising their clinical judgement. This guidance does not, however, override the individual responsibility of health professionals to make appropriate decisions in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

Implementation and Audit

- All clinicians with responsibility for treating adults with epilepsy should review their current practice and policies to take account of the guidance.
- Local guidelines, protocols or care pathways that refer to the care of adults with epilepsy should incorporate the guidance.
- To measure compliance locally with the guidance, the following criteria could be used and will be applicable to all individuals with epilepsy. Further details on suggestions for audit are presented in Appendix C of the original guideline document.
    - A person with epilepsy is treated with a newer antiepileptic drug in the following circumstances.
        - He or she has not benefited from treatment with the older antiepileptic drugs such as carbamazepine or sodium valproate.
    - Older antiepileptic drugs are unsuitable because:
        - there are contraindications to the drugs
        - they could interact with other drugs the person is taking (notably oral contraceptives)
        - they are already known to be poorly tolerated by the individual
        - the person is a woman of childbearing potential (see "Major Recommendations" field in this summary).
    - A person with epilepsy is ordinarily treated with a single antiepileptic drug. If treatment with a single antiepileptic drug (monotherapy) is unsuccessful, then the person is treated using another single antiepileptic drug, exercising caution during the changeover period.
    - A person with epilepsy is prescribed combination adjunctive) therapy only when attempts at monotherapy with antiepileptic drugs have not resulted in seizure freedom. If trials of adjunctive therapy do not bring about worthwhile benefits, the person's treatment is reverted to the regimen that has proved most acceptable to the patient in terms of its effectiveness in reducing seizure frequency and the tolerability of its side effects.
    - In women of childbearing potential, the risk of the drugs causing harm to an unborn child and the possibility of interaction with oral contraceptives are discussed between the woman and the responsible clinician and an assessment is made as to the risks and benefits of treatment with individual drugs.
    - A person who has had a first seizure is seen as soon as possible by a specialist in the management of epilepsies.
    - Treatment is reviewed at regular intervals.
- Local clinical audits also could include measurement of compliance with issues identified in the National Clinical Audit of Epilepsy-related Death and/or Improving Services for People with Epilepsy (the Department of Health response to the National Clinical Audit of Epilepsy-related Death), such as carrying out appropriate investigations to reach a diagnosis of epilepsy, supporting people who are having problems with their drug regimens, and shared-care arrangements. Local audits may be able to make use of data already being collected for registries on epilepsy.

IMPLEMENTATION TOOLS

Audit Criteria/Indicators
Patient Resources
Quick Reference Guides/Physician Guides

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness
Safety

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

National Institute for Clinical Excellence (NICE). Newer drugs for epilepsy in adults. London (UK): National Institute for Clinical Excellence (NICE); 2004 Mar. 36 p. (Technology appraisal; no. 76).

ADAPTATION

Not applicable: The guideline was not adapted from another source.

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GUIDELINE COMMITTEE

Appraisal Committee

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) format from the National Institute for Health and Clinical Excellence (NICE) Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Newer drugs for epilepsy in adults. Quick reference guide. London (UK): National Institute for Health and Clinical Excellence (NICE); 2004 Mar. 2 p. (Technology appraisal 76). Available in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence (NICE) Web site.
- A rapid and systematic review of the clinical effectiveness, tolerability and cost effectiveness of newer drugs for epilepsy in adults (Commercial-in-confidence [CIC] data removed). Assessment report. Centre for Reviews & Dissemination (CRD)/Centre for Health Economics (CHE); 2003 Feb. 1024 p. Available in Portable Document Format (PDF) from the NICE Web site.

Print copies: Available from the National Health Service (NHS) Response Line 0870 1555 455. ref: N0453. 11 Strand, London, WC2N 5HR.

Additionally, Audit Criteria can be found in Appendix C of the original guideline document.

PATIENT RESOURCES

The following is available:

- Newer drugs for epilepsy in adults. Understanding NICE guidance - information for adults with epilepsy, their families and carers, and the public. London (UK): National Institute for Health and Clinical Excellence (NICE); 2004 Mar. 10 p. (Technology appraisal 76).

Electronic copies: Available in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence (NICE) Web site.

Print copies: Available from the Department of Health Publications Order Line 0870 1555 455. ref: N0454. 11 Strand, London, WC2N 5HR.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

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